MEDICAL STAFF CONFERENCE

Hyperlipemia, Abdominal Pain and Growth Retardation

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. LAWRENCE BASSO*: The patient was a nine-year-old white boy admitted for evaluation of hyperlipemia. For two years he has had recurrent left upper quadrant abdominal pain associated with vomiting. On examination elsewhere, shortness of stature, splenomegaly and lipemia retinalis were noted. The blood was pink and the serum grossly lipemic. It separated into creamy supernatant and relatively clear infranatant layers on ordinary centrifugation, a finding consistent with predominant chylomicronemia. The serum triglyceride level four months before the patient was admitted was 1,400 mg per 100 ml. The patient has had no appreciable linear growth since age six and is now shorter than his seven-year-old sister. His learning ability, however, appears to be on a par with that of his other siblings.

On physical examination, he appeared normally developed although of short stature. His height was 117 cm and his weight was 21 kg. Significant negative findings included absence of xanthomata and lipemia retinalis, normal tonsils and absence of significant lymphadenopathy. The spleen was firm and greatly enlarged, the tip extending nearly to the iliac crest. The liver was not enlarged.

Laboratory data were as follows: Hematocrit 28 per cent; leukocytes 3,200 and platelets 80,000 per cu mm of blood and reticulocytes 1 per cent. Red blood cells were microcytic and hypochromic. No abnormality was seen on a smear of sternal marrow. Serum iron was 58 mg per 100 ml and total iron-binding capacity was 495 mg per 100 ml of blood. After a low fat diet and oral iron therapy were begun, the hematocrit was unchanged but the leukocyte count rose to 7,200 per cu mm of blood, platelets to 200,000 and reticulocytes to 4.8 per cent. A guaiac examination of stool initially was positive but reverted to negative when a myoglobin-free diet was given. No stainable fat was present in the stool. Liver function studies were within normal limits as was the creatinine clearance and serum protein-electrophoresis. Calcium was 9.4 mg per 100 ml and phosphorus 4.5 mg per 100 ml of blood.

Results of growth hormone studies were as follows: Following intravenous administration of 0.2 units of insulin per kg of body weight, serum growth hormone level rose from 3 mμg per ml to 5 mμg per ml. Similar results have been obtained by Kaplan[7] and co-workers in children with growth retardation but with no other laboratory evidence of hypopituitarism. In adults, a rise to at least 15 mμg per ml is normal. The oral glucose tolerance test, insulin tolerance test and the Himsworth test (an oral glucose-insulin tolerance test) were all within normal limits. The patient's bone age was retarded to about seven years. X-ray films of the skull showed a normal sella turcica. An upper gastrointestinal series showed no abnormality and the small bowel pattern was normal. An intravenous pyelogram showed a curious anomaly of

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TABLE 1.—*Per Cent Composition of Plasma Lipoprotein-Lipids*

	Cholesterol Esters	*Free Cholesterol*	*Phospholipids*	*Triglycerides*
Chylomicrons	6	3	7	83
Very low density lipoproteins	18	7	19	56
Patients' lipoproteins (d<1.006)	9	3	9	79

the left kidney which was probably a variant of a horseshoe kidney.

Serum lipoproteins were separated in the preparative ultracentrifuge. The composition of the density less than 1.006 fraction (chylomicrons plus very low density lipoproteins) closely resembled that of pure chylomicrons (Table 1). Very little lipid was present in the low density (1.006-1.063) and high density (1.063-1.21) lipoproteins.

With the patient on a diet containing less than 0.1 gm of fat per kg of body weight daily, the serum triglyceride level fell rapidly and the serum cleared. On the third day of this diet, the triglyceride level was about 200 mg per 100 ml. After the patient had been on the diet for four days, he was given a single meal containing 36 gm of fat. Within 12 hours, the serum triglyceride level rose from 180 mg per 100 ml to about 1,000 mg per 100 ml (Chart 1). Twenty-four hours after the single fat meal, the serum triglycerides were almost 500 mg per 100 ml. After two days, the serum triglycerides were still elevated and visible lipemia extended from two hours to 72 hours after the fat meal.

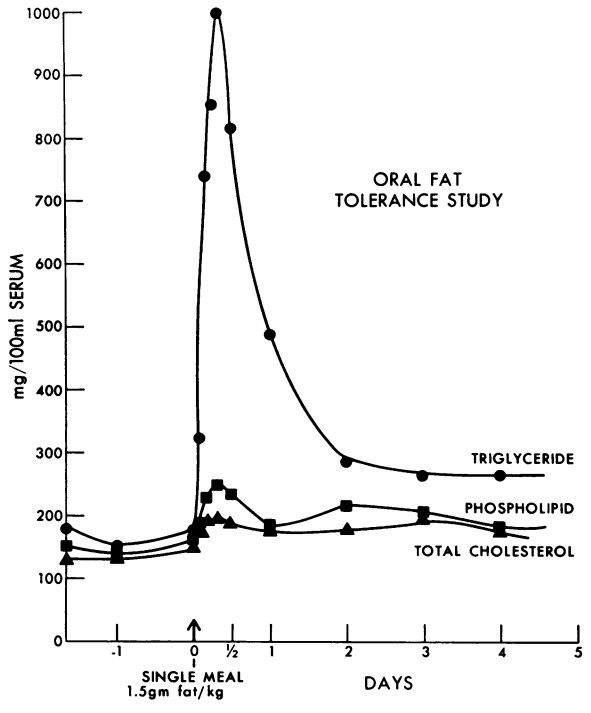

Chart 1.—Effect of a single fat-rich meal on serum lipid levels. (Except for this meal, the patient's diet contained less than 3 gms of lipids daily during the period shown).

DR. LLOYD H. SMITH, JR.*[1]: This patient and the general problem of hyperlipemia will be discussed today by Dr. Richard J. Havel, Professor of Medicine and Associate Director of the Cardiovascular Research Institute at the University of California Medical Center.

DR. RICHARD J. HAVEL: This patient's disorder is an example of one variety of hereditary hyperlipemia, but some features of his illness have not been previously reported in this syndrome. The condition, first described by Bürger and Grütz,[2] consisted of hyperlipemia with good response to fat restriction. Later, a detailed description was written by Holt[6] and his collaborators at Johns Hopkins. Although eruptive xanthomata were present in the case described by Bürger and Grütz, we have not seen them in this particular variety of essential hyperlipemia. Hepatosplenomegaly is frequently seen, particularly in children. The splenomegaly in the patient presented today is more pronounced than any reported previously to my knowledge. More commonly, the spleen is palpable just below the left costal margin.

Another feature which is also common in other forms of essential hyperlipemia is acute abdominal crisis. Often, recurrent abdominal pain, which is common in childhood and less severe during adolescence, recurs in adult life. Seldom have these abdominal crises in childhood been diagnosed as pancreatitis, and in the patient presented today we have had no clear documentation that he has had pancreatitis. In view of the very large spleen, it is possible that splenic infarcts were the cause of the left upper quadrant abdominal pain.

Growth failure has not been described in this syndrome but the patient in the present case wears the same shoes and the same clothes that he did when he was six years old; his bone age is that of a seven-year-old. At present, we can only speculate on the cause of this growth failure. Possibly, hypersplenism and associated rapid turnover of hematopoietic tissues have taken precedence over

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utilization of amino acids for somatic growth. In addition, his diet has probably been inadequate. This is shown by the iron deficiency, which cannot be attributed to gastrointestinal blood loss. Leukopenia, which was present on admission, disappeared in association with one or both of two procedures in the hospital—iron therapy and restriction of fat in the diet. Long-term iron deficiency can be associated with leukopenia but is seldom associated with thrombocytopenia of the degree observed here. It is tempting to speculate that phagocytosis of chylomicrons in the spleen may be important in the pathogenesis of the hypersplenism.

I would like to turn to a discussion of the basic disease process exemplified by this patient, namely, a variety of hereditary hyperlipemia resulting from deficiency of the enzyme, lipoprotein lipase. In evaluating a child with hyperlipemia, it is important to eliminate known causes such as uncontrolled diabetes, glycogen storage disease and nephrotic states; and, more rarely, myxedema, Niemann-Pick's disease and diffuse lipo-atrophy. In the absence of these conditions, the presence of hyperlipemia suggests a group of diseases usually called "essential hyperlipemia." When this syndrome is seen in childhood, the particular disease we are discussing today is the most common form; however, it is a rare condition in the spectrum of essential hyperlipemia seen in adults. The next question of importance is the type of hyperlipemia. Is it chylomicronemia or endogenous hyperlipemia?

Table 2 shows several lipoprotein fractions which can be separated by a variety of physical techniques. Chylomicrons and the very low density lipoproteins, which are the two major triglyceride-bearing lipoproteins in blood plasma, are less dense than the non-protein solvent density of plasma, namely 1.006. With ultracentrifugation of plasma at its own density, these two fractions will float to the top of the tube. The chemical composition of the abnormal lipoprotein in the present case was close to that of chylomicrons. Chylomicrons, being larger and less dense molecules than the very low density lipoproteins, tend to separate more readily as a cream layer, as was well demonstrated in this patient. Quite clearly he had predominantly a chylomicronemia. The very low density lipoproteins, which carry endogenous triglycerides, can accumulate in the plasma as a result of defective removal mechanisms or as a result of increased secretion from the liver. Whenever chylomicronemia predominates, the problem is generally that of defective removal. The normal mechanisms for clearing chylomicron triglycerides from the blood are so efficient that they can accommodate 200 to 400 gm of fat daily. When chylomicrons accumulate and persist from meal to meal, deficient removal mechanisms should be suspected.

TABLE 2.—*Lipoprotein Classes in Human Blood Plasma*

Class	*Density*	*Molecular Diameter (Ångströms)*	*Electrophoretic Mobility (starch gel)*
Chylomicrons	..~0.96	500-10,000	Variable, α to β
Very low density lipoproteins	..0.96-1.006	200-1,000	α_2 or "pre-β
Low density lipoproteins	..1.006-1.06	200	β
High density lipoproteins	..1.06-1.21	100	α_1

Patients with defective removal mechanisms will respond to restriction of dietary fat. In cases resembling the present one, reported several years ago, three of six siblings had this syndrome.[4] Neither parent had lipemia. This family lived on a farm in Maryland and ate large amounts of eggs and chicken. The childrens' plasma was lipemic when they entered the Clinical Center at the National Institutes of Health. When they were placed on a standard 1 gm per kg fat diet, (about a 70 gm fat diet for an adult), they had a very predictable triglyceride level, approximately 1,000 mg per 100 ml. When fat was eliminated from the diet, the lipemia disappeared in two to three days and single fat meals produced a very abnormal fat-tolerance curve. The effect of heparin was slight or absent in contrast to the response seen in other types of hyperlipemia. Two of the siblings in this family had had recurrent attacks of abdominal pain. When fat was restricted, all the lipoprotein lipids of density less than 1.006 fell and non-triglyceride constituents of lipoproteins accumulated in the low density lipoprotein fraction. For this reason cholesterol and phospholipid levels tend to fall less than do triglyceride levels when such patients are placed on a low fat diet.

The dramatic response to dietary fat in patients with this syndrome distinguishes it from other

forms of hyperlipemia which are primarily endogenous in nature and which usually do not respond well to fat restriction. In fact, in the so-called carbohydrate-induced form, the hyperlipemia is aggravated by restriction of dietary fat. The problem we are dealing with today, then, is one of removal of chylomicrons from the blood. This process is defective in patients with this disease because of deficient removal mechanisms.

Chylomicrons are large spherical particles, approximately 3,000 Ångströms in diameter. The very low density lipoproteins containing endogenous triglycerides are about 300 Ångströms in diameter (Table 2). Their metabolism qualitatively is similar to that of chylomicrons.[5] When secretion of triglycerides from the liver is increased, as in pregnancy, a striking endogenous hyperlipemia may develop in patients with this syndrome. Chylomicrons are so large that they cannot readily pass the endothelial barrier of capillaries and there is little evidence that pinocytotic mechanisms are involved in their transport. For these reasons, much work has been devoted to the study of mechanisms by which large quantities of lipid constituents of chylomicrons can traverse the capillary wall efficiently.

One of the first hints about this mechanism was obtained when chylomicrons were collected from animals which had been fed labeled fatty acids. When such chylomicrons or endogenous lipoproteins rich in C^{14}-labeled triglycerides are injected into animals, rapid removal of the triglycerides occurs with a half-time of five to 15 minutes. A very rapid appearance of the radioactivity injected in the form of triglyceride fatty acids is seen in an unesterified form, the so-called free fatty acids which are carried in the plasma bound to albumin. There is a rapid peaking of radioactivity and then a gradual decrease in the free fatty acids, roughly parallel to the disappearance curve for the triglyceride fatty acids. This indicates that, in association with the removal process, there is a chemical reaction which results in hydrolysis of the triglycerides to yield free fatty acids.

It was shown a number of years ago by Hahn that lipemia rapidly disappears when heparin is given to a lipemic dog. We now know that this is the result of liberation of an enzyme from tissues into the blood. This lipase is called clearing-factor lipase in Great Britain, and lipoprotein lipase in this country. Lipoprotein lipase catalyzes the hydrolysis of triglycerides, either in the form of chylomicrons (exogenous triglyceride) or in the form of very low density lipoproteins (endogenous triglycerides), in order to release free fatty acids and glycerol. This reaction is thought to account for the rapid hydrolysis observed when labeled chylomicron triglycerides are given intravenously.

There is other evidence that this enzyme is responsible for the hydrolytic process. First of all, as I have mentioned, when one administers heparin, lipemia clears rapidly as the enzyme is liberated into the blood. Conversely, injection of protamine into a lipemic animal decreases the rate of removal of chylomicrons. Protamine can also induce and maintain lipemia in fasted animals and there is evidence that this occurs because of inhibition of removal mechanisms for endogenously-produced triglycerides. It is known from studies *in vitro* that protamine inhibits lipoprotein lipase. Furthermore, the ability of tissues to take up chylomicron triglyceride fatty acids from the blood correlates very closely with the activity of lipoprotein lipase in that tissue. This is shown best in the case of adipose tissue, in which lipoprotein lipase activity varies strikingly with the nutritional state. After glucose ingestion, a large amount of enzyme activity is extractable from adipose tissue in both rats and rabbits. In the fasting state, this tissue contains very little enzyme activity. If labeled triglycerides are injected into rats or rabbits which have been fed, the triglyceride fatty acids accumulate in the adipose tissue; in contrast, in the fasting animal almost none of the triglyceride fatty acids are found in the tissue. For example, when triglycerides in which palmitate has been labeled with C^{14} are injected into fasting rabbits, only 1 to 3 per cent of the radioactivity is found in the total adipose tissue after two hours. In fed rabbits, virtually half of the injected radioactivity is found in the total adipose tissue at this time. This has also been shown *in vitro*. Dr. Alyce Bezman-Tarcher, Dr. James M. Felts and I demonstrated that incubation of labeled lipoproteins with adipose tissue from fed animals led to brisk uptake. This was shown to be well correlated with the enzyme activity extractable from the same tissue. This is further cogent evidence, albeit indirect, that lipoprotein lipase is involved in the removal process.

A number of years ago on the basis of the data which I have shown you, we and others pos-

tulated that the enzyme, lipoprotein lipase, acts primarily at the level of the capillary wall. In recent electron microscopic studies, it has not been possible to demonstrate transport of intact chylomicrons across capillaries. Electron micrographs have shown chylomicrons "sticking" at the surface of capillaries in adipose tissue where we believe the enzyme lipoprotein lipase to be located. Chart 2 demonstrates in more detail our current concept of how the fatty acid constituents of triglycerides pass across capillary membranes. At the capillary surface, an enzyme-substrate complex forms, hydrolysis then occurs, and the fatty acids released either circulate in the blood, bound to albumin, or are transported by a carrier mechanism into the cell where they can be esterified to form triglycerides. In the case of other tissues such as muscle, this same reaction can occur. In these tissues the fatty acids can then be burned in the mitochondria to supply the demands of cellular metabolism.

Additional evidence which suggests that the enzyme is located at some site very close to the capillary surface is the following: If heparin is injected into the femoral artery of an animal in which the femoral vein of the same side has been cannulated, enzyme activity appears in the femoral vein blood within seconds. It is very difficult to visualize how a molecule such as heparin, with

ASSIMILATION OF TRIGLYCERIDE FATTY ACIDS BY ADIPOSE TISSUE

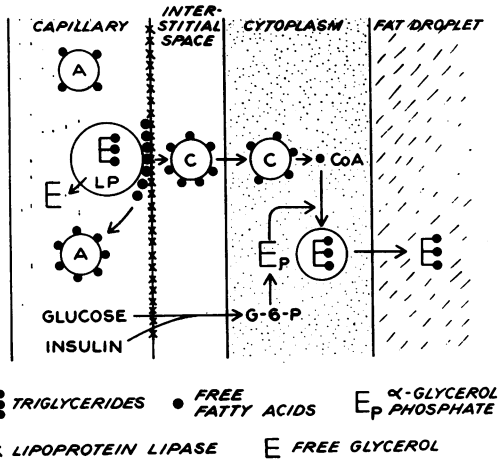

Chart 2.—Postulated mechanism for transporting and storing fatty acid constituents of plasma triglycerides in adipose tissue. This chart was obtained from *Fat as a Tissue*, edited by Rodahl and published by McGraw-Hill Company in 1964, and is reproduced with their kind permission. A = Ångströms. C = Carbon. G-6-P = Glucose-6-phosphate.

a molecular weight of about 15,000, could gain access to the cell parenchyma and release the enzyme so that it could appear in the blood in a single circulation.

With this evidence that lipoprotein lipase may be essential for normal removal of chylomicrons, we would certainly suspect that deficiency of this enzyme could account for the type of hyperlipemia shown in the patient presented today. This has, in fact, been observed; it was first shown in the previously mentioned family that was studied at the National Institutes of Health. Assay of lipoprotein lipase activity in blood plasma is performed as follows: A standard amount of heparin is injected intravenously and samples of blood are obtained at various periods of time (usually 10 minutes) after injection. The plasma is separated and incubated under conditions conducive to optimal enzyme activity. An excess of albumin is added to accept the fatty acid liberated. A substrate, usually coconut oil emulsion, is also added in excess.[3] Coconut oil is a peculiar oil; its triglycerides contain primarily lauric acid, a C-12, saturated fatty acid. Normal chylomicron triglycerides contain predominately C-16 and C-18 fatty acids, either saturated or unsaturated. However, coconut oil triglycerides are readily hydrolyzed by lipoprotein lipase. The three affected siblings in the family previously described had very low activities of lipoprotein lipase in plasma after the injection of heparin, whereas two subjects with endogenous forms of hyperlipemia, not associated with predominant chylomicronemia, had normal enzyme activity.

To determine if the intrinsic activity of the enzyme was low in the affected siblings or whether the low activity resulted from presence of inhibitors or lack of activation in the subjects' plasma, the following studies were done. Pre-heparin and post-heparin plasma from normal subjects was mixed with plasma from subjects with hyperlipemia. Pre-heparin plasma from hyperlipemic subjects did not inhibit lipolytic activity of the post-heparin plasma from normal subjects. Enzyme activity could not be increased by adding pre-heparin plasma from normal subjects to the patient's post-heparin plasma. Thus, there appeared to be a true defect in the activity of the enzyme rather than one resulting from extraneous factors in the plasma.

To determine whether the chylomicrons of the hyperlipemic subjects were abnormal, a high fat

diet was fed to one of the hyperlipemic subjects and chylomicrons were harvested from the plasma. These chylomicrons were then injected into a normal subject and a hyperlipemic sibling, who were on a low-fat diet at the time of the study. The injections were given on three separate days. On the first day, a standard amount of chylomicrons was injected; the normal subject removed them with a half-time of 17 minutes (a normal value), whereas the subject with hyperlipemia required 100 minutes to remove half of the chylomicrons from the blood. Therefore, the substrate behaved normally when exposed to normal mechanisms for removal. We were also able to increase the removal rate with heparin and decrease it by pre-treatment with protamine sulfate in the normal subject. As expected, this could not be done in the subject with presumed deficiency of the enzyme. This provided confirmatory evidence that the enzyme was not only deficient in post-heparin plasma but could not be activated normally for *in vivo* functions.

Assay of lipoprotein lipase in the patient presented today is shown in Table 3. This assay was done using an artificial emulsion containing soy bean oil, which consists primarily of C-16 and C-18 saturated and unsaturated fatty acids, as described by Boberg and Carlson.[1] Under these conditions, the nature of the triglyceride being attacked by the enzyme is similar to that contained in chylomicrons. Additionally, in contrast to the commonly used coconut oil emulsion (Ediol®), it contains no monoglycerides. Since there is evidence that more than one lipase may be present in post-heparin plasma, it is possible that the nature of the substrate affects the specificity of the assay for lipoprotein lipase. Values of lipoprotein lipase were about 25 per cent of normal in the patient presented today. Lipoprotein lipase obtained from adipose tissue is effectively and almost completely inhibited by 0.5 molar sodium chloride. When we use coconut oil emulsion as a substrate in post-heparin plasma, we obtain variable inhibition with 0.5 molar sodium chloride. Using soy bean emulsion, we obtain about 80 per cent inhibition. In the hyperlipemic subject, no inhibition of enzyme activity was produced by 0.5 molar sodium chloride. It is possible, therefore, that the small enzyme activity in the patient's plasma is not lipoprotein lipase but a separate enzyme which has activity toward soy bean oil triglycerides. This seems reasonable because it is unusual to find 25 per cent of normal enzyme activity in a homozygous state which is presumably determined by a recessively-transmitted gene.

TABLE 3.—*Lipoprotein Lipase Assay of Plasma in Present Case (Method of Boberg and Carlson)*

	Enzyme Activity (μEq per minute and per ml of plasma)	
	Normal Values	*Patient*
In standard buffer	~0.2	0.05
In standard buffer +0.5 M NaCl	~0.04	0.06
Activity inhibited by 0.5 M NaCl	~0.16	nil

I will conclude by referring to the question of pancreatitis and hyperlipemia. We have studied three additional patients with this particular form of hyperlipemia who had clearly documented pancreatitis. In one a pancreatic pseudo-cyst developed, another had acute hemorrhagic pancreatitis with shock and tetany, and a third had diffuse pancreatic calcifications. In all cases, recurrent attacks of pancreatitis can be prevented. As first shown by Klatskin and Gordon,[8] the attacks are completely prevented by restricting dietary fat. This usually requires a diet containing about 30 gm of fat per day.* When triglyceride levels remain less than 500 to 600 mg per 100 ml, we have never seen attacks of pancreatitis in hyperlipemic subjects. In some cases, attacks of pancreatitis can be produced at will by feeding fat.

We have considered the following possible mechanisms as a result of the demonstration by several investigators that free fatty acids activate certain clotting factors and tend to produce thrombosis. This is particularly true for saturated fatty acids such as palmitic acid and stearic acid. Although it is not certain how these fatty acids interact with the clotting mechanism, there is evidence that they activate either plasma thromboplastin antecedent (PTA) or Hageman factor or possibly both. In the presence of hypertriglyceridemia, whether as chylomicronemia or as very low density hyperlipoproteinemia, large amounts of substrate are available for lipase action. Leakage of small amounts of lipase from pancreatic cells into the pancreatic capillaries could result in intense lipolysis and release of fatty acids locally which could activate the clotting mechanism and cause thrombosis. The fatty acids might also interact with calcium to form insoluble soaps. Since

*In other forms of essential hyperlipemia, other measures which reduce triglyceride levels, such as restriction of caloric intake, will prevent pancreatitis.

calcium ion is involved in the normal integrity of the capillary wall, capillary damage could result. These phenomena might lead to further release of pancreatic lipase, producing a self-intensifying process. Although there is no direct evidence for this hypothesis, it does provide an explanation for the relation between the degree of hypertriglyceridemia and the occurrence of pancreatitis. I will mention in closing that hyperlipemia can also result from pancreatitis. In those cases in which transitory hyperlipemia is associated with pancreatitis, the patient is usually a severe alcoholic. Abstaining from alcohol generally leads to subsidence of both pancreatitis and hyperlipemia.

DR. KENNETH L. MELMON*[2]: I was fascinated by your proposal for pathogenesis of pancreatitis which stressed an important step—activation of Hageman factor. As you know, this reaction is also important in the activation of kallikrein. The latter has been implicated, either in the pathogenesis or as a result of pancreatitis. Investigations have attempted to correlate the arterial content of kallikrein and the peptides such as bradykinin with the manifestations of pancreatitis. Some groups feel that kinin release may be responsible for the flush and hypotension seen with the disease.

DR. HAVEL: As I recall, I think that Dr. Oscar Ratnoff feels that it is not Hageman factor but plasma thromboplastin antecedent (PTA) that is activated by fatty acids. But this is a point for the experts. Thank you for that suggestion.

DR. WILLIAM A. ATCHLEY*[3]: As a newcomer in this field, having been in it for about an hour or so, I wonder if heparin physically alters the enzyme which is already present in the blood?

DR. HAVEL: That was the original thought for the heparin effect. However, addition of heparin to lipemic plasma does not activate lipolysis. Heparin must circulate through a capillary bed in order to obtain a substance in the plasma which can be purified as a protein.

DR. ATCHLEY: Is there a temperature optimum?

DR. HAVEL: Yes, the temperature optimum is 37°C (98.6°F), the pH optimum is about 8.6 and it is inactivated by heat. It is absorbed, like prothrombin, on calcium phosphate gel and eluted with citrate. In this way, it can be purified substantially. It has all the qualities of an enzyme and we know that it activates the hydrolytic process. It is conceivable that another substance is released from capillaries by heparin which then activates a plasma lipase. Unfortunately, it has thus far not been possible to purify the enzyme to an extent which will allow study of its kinetic behavior.

DR. HIBBARD E. WILLIAMS*[4]: Is it possible that there is an inability of the tissue to respond to heparin?

DR. HAVEL: Lipoprotein lipase activity is regularly released from normal human adipose tissue incubated with heparin.[9] In 1962, we assayed adipose tissue from one of our subjects with abnormally low activity in post-heparin plasma and could detect none.

DR. EUGENE EISENBERG*[5]: Do you think this patient's failure to grow is secondary to the hyperlipemia or to the inability to transport fatty acids?

DR. HAVEL: I doubt that as regards energy needs of tissues, it results from the inability to transport fatty acids. The ability to mobilize fatty acids from adipose tissue and burn them elsewhere persists. Intermediary metabolism in general appears to be normal. I think it is more likely that uptake of chylomicrons in the spleen is in some way related to the growth failure. This is speculation. The patient appears to have normal pituitary function, since there are readily detectable levels of growth hormone in plasma. The slight increase in plasma growth hormone after insulin may not be a reliable indicator of growth hormone deficiency in children.[7] It will be interesting to follow the linear growth of this patient while on a fat-restricted diet.

EDITOR'S NOTE: In the seven months following discharge from hospital, during which time the patient has been maintained on a fat-restricted diet, he has grown 4 cm in height. The spleen has become much smaller. It now extends only to the level of the umbilicus, and the splenic notch is no longer palpable.

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